Second-trimester Molecular Prenatal Diagnosis of Sporadic Apert Syndrome Following Sonographic Findings of Mild Ventriculomegaly and Clenched Hands Mimicking Trisomy 18

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Apert syndrome (OMIM 101200) is a congenital disorder characterized by acrocephaly, craniosynostosis, midface hypoplasia, and syndactyly of the hands and feet [1]. The reported prevalence of Apert syndrome at birth has ranged from 1 in 160,000 [2] to 1 in 64,500 births [3]. The majority of cases of Apert syndrome arise sporadically as the result of a *de novo* mutation in the sperm, associated with a paternal age effect; only a few cases are inherited from affected parents in an autosomal dominant pattern [4,5]. Apert syndrome is caused by mutations in the fibroblast growth factor receptor 2 (*FGFR2*) gene (OMIM 176943) located at 10q26. Two mutations of Ser252Trp (S252W) and Pro253Arg (P253R) account for over 98% of cases of Apert syndrome [6,7].

Although cases of prenatally diagnosed Apert syndrome have been reported, many cases remain undiagnosed until delivery, or are diagnosed in late gestation when polyhydramnios and craniofacial deformities become evident. Syndromes involving craniosynostosis may be associated with abnormalities of the digits. Crouzon syndrome is associated with normal hands and feet. Jackson-Weiss syndrome is associated with normal hands, medially deviated broad great toes and cutaneous syndactyly of the second and the third toes. Apert syndrome is associated with symmetric syndactyly of the hands and feet. Pfeiffer syndrome is associated with broad abducted thumbs, broad great toes, and brachymesophalangy and partial syndactyly of the hands and feet. In cases with mild ventriculomegaly, a thorough examination of the hands in the second trimester may lead to a specific diagnosis of Apert syndrome, as in the current case.

A 30-year-old, gravida 1, woman was referred to Mackay Memorial Hospital for amniocentesis at 21 weeks of gestation because of mild ventriculomegaly and clenched hands detected on prenatal ultrasound. Her husband was 32 years of age. She and her husband were both healthy and unrelated, and there was no family history of congenital malformations. Prenatal ultrasound at 18 weeks of gestation revealed a male fetus with fetal biometry equivalent to 18 weeks, a normal skull shape, mild ventriculomegaly, and clenched hands (Figures 1 and 2). Trisomy 18 was highly suspected. Amniocentesis was performed at 21 weeks of gestation. Conventional cytogenetic analysis revealed a 46,XY karyotype. Oligonucleotide-based array comparative genomic hybridization using uncultured amniocytes demonstrated no deletions or duplications.

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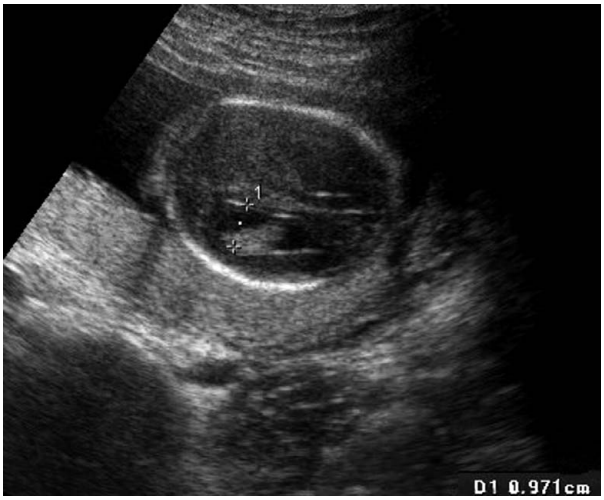

Figure 1. Mild ventriculomegaly with a normal skull shape on prenatal ultrasound at 18 weeks of gestation.

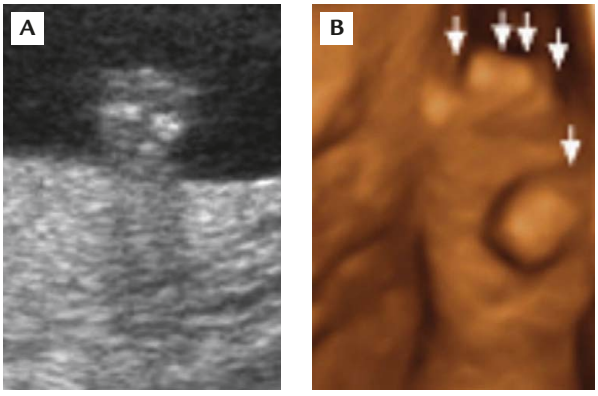

Figure 2. (A) Two-dimensional ultrasound demonstration of a clenched hand at 18 weeks of gestation. (B) Three-dimensional ultrasound demonstration of a mitten hand with a broad thumb and second-to-fourth-finger syndactyly (arrows) at 24 weeks of gestation.

DNA testing for Apert syndrome was performed at 24 weeks of gestation using amniocytes. A heterozygous c.755 C > G, TCG > TGG transversion leading to a Ser252Trp (S252W) mutation in the *FGFR2* gene was found in the fetus (Figure 3). The mutation was not present in either of the parents. Three-dimensional ultrasound examination demonstrated a mitten hand with second-to-fourth-finger syndactyly and a broad proximally deviated thumb, midface hypoplasia and low-set ears (Figures 2 and 4). The findings were consistent with Apert syndrome. The pregnancy was subsequently terminated and a dead 1,082-g fetus was delivered with prominent midface hypoplasia, low-set ears, bilateral mitten syndactyly of the hands and feet, and broad and proximally displaced thumbs and big toes (Figures 5 and 6).

Arthrogryposis, overlapping fingers, rocker-bottom feet and talipes are frequently associated with trisomy

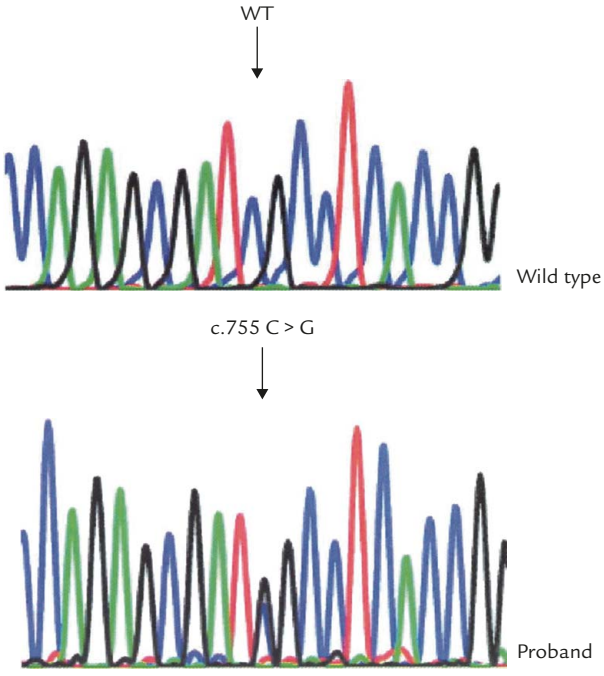

Figure 3. DNA testing showed a c.755 C > G, TCG > TGG, or S252W mutation in the proband. WT = wild type for internal control.

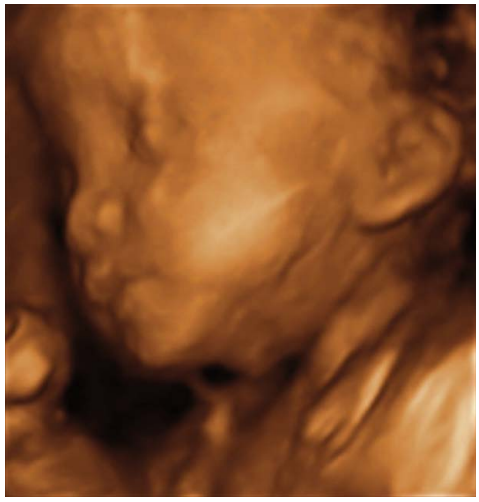

Figure 4. Three-dimensional ultrasound demonstration of midface hypoplasia and a low-set ear at 24 weeks of gestation.

18 [8]. Snijders et al [9] found that abnormalities of the hands and feet were diagnosed in 72% of fetuses with trisomy 18. Ventriculomegaly has been associated with chromosome abnormalities, genetic defects, intrauterine hemorrhage, infections, and neural tube defects [10]. Snijders et al [9] reported that chromosome abnormalities occurred in 13% of cases with ventriculomegaly. They also reported that ventriculomegaly occurred in 14% of cases with trisomy 18. Prenatal diagnosis of clenched hands and mild ventriculomegaly in the second trimester, as in the current case, increases

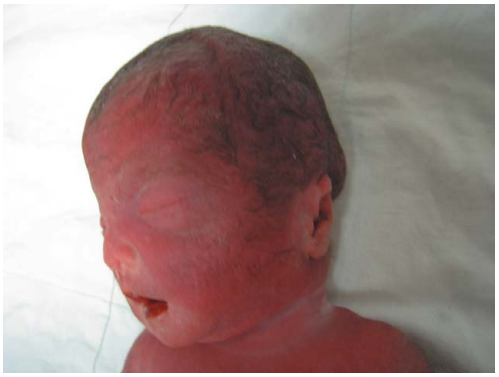

Figure 5. Corresponding craniofacial appearance at birth.

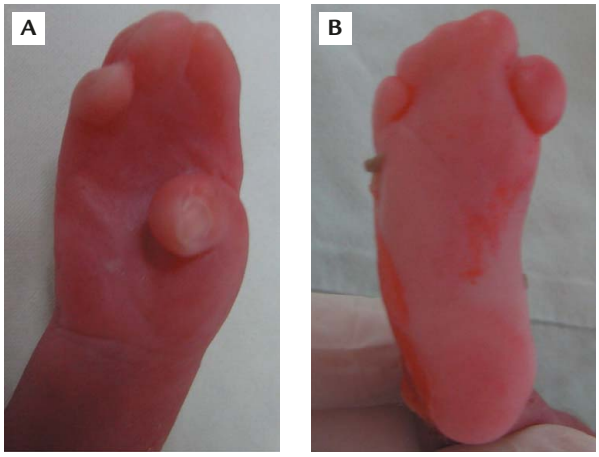

Figure 6. (A) A mitten hand and (B) a mitten foot with second-to-fourth-digit syndactyly and a broad proximally deviated thumb (great toe).

suspicion of fetal aneuploidy, such as trisomy 18. In this presentation, subsequent DNA testing and three-dimensional ultrasound examination following cytogenetic investigation to exclude aneuploidy led to a correct prenatal diagnosis of Apert syndrome. This case emphasizes the need for a thorough analysis of the fetal hands and skull in cases with prenatally detected mild ventriculomegaly.

Central nervous system anomalies associated with Apert syndrome include ventriculomegaly (48.5%), hydrocephalus (9%) and agenesis or hypogenesis of the corpus callosum, or posterior fossa anomalies (21%) [11]. In a study of 113 cases of Apert syndrome, Cohen and Kreiborg [12] found 14 with non-progressive ventriculomegaly, six with hydrocephalus, nine with partial absence of the septum pellucidum, and 15 with complete agenesis of the corpus callosum. In a study of 60 cases of Apert syndrome, Renier et al [13] found 35 with non-progressive ventriculomegaly, eight with hydrocephalus, 30 with partial absence of septum pellucidum, three with complete agenesis of the corpus callosum, and 27 with partial agenesis of the corpus callosum. In a study of 18 cases of Apert syndrome, Yacubian-Fernandes et al [14] found five with non-progressive ventriculomegaly, seven with partial absence of septum pellucidum, and five with complete agenesis of the corpus callosum. In a study of 30 cases of Apert syndrome, Quintero-Rivera et al [15] found 23 with non-progressive ventriculomegaly, four with hydrocephalus, 12 with partial absence of septum pellucidum, two with complete, and one with partial agenesis of the corpus callosum. Quintero-Rivera et al [16] reported that a common S252W mutation and mild dilation of the lateral cerebral ventricles and complete agenesis of the corpus callosum were diagnosed by prenatal ultrasound and magnetic resonance imaging in two of 30 patients with Apert syndrome. David et al [17] reported that three of five fetuses with Apert syndrome detected by second-trimester ultrasound had brain anomalies, including ventriculomegaly in two fetuses and enlarged cisterna magna in one fetus. It has been reported that 97% of cases of Apert syndrome have second-to-fifth-finger syndactyly and 3% of the cases have second-to-fourth-finger syndactyly [18]. Apert syndrome should be included in the differential diagnosis in the event of mild ventriculomegaly with hand abnormalities. Because cytogenetic analysis by amniocentesis is routinely recommended for the evaluation of chromosome abnormalities under such circumstances, simultaneous DNA testing for mutations in the *FGFR2* gene should be considered if the cytogenetic result is normal.

Acknowledgments

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